Remarks

Claims 2-3, 6-28, and 30-36, and 38-42 are pending. Claim 2 has been amended. Claims 43-45 have been added.

Applicants presume that the rejection of claims 2, 17, 19, 21, 23, 25, 32, 34 and 36 under 35 U.S.C. § 112, second paragraph was withdrawn in response to Applicants amendments.

Rejection Under 35 U.S.C. § 112, first paragraph

A. Claims 2-3, 6-28, and 30-36, and 38-42 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. In support of this rejection, the Office Action makes several assertions that constitute factual and legal error.

1. First, the Office Action continues to incorrectly apply caselaw relating to the written description requirement to the instant claims. For example, the Office Action again cites *Fiddes v. Baird* to support the argument that the specification fails to recite a representative number of species defined by structure and function such that the skilled artisan could not envision the claimed compositions. However, the facts in *Fiddes v. Baird* are not applicable to the instant claims. Applicants in *Fiddes v. Baird* claimed a DNA sequence encoding mammalian FGF but only taught a DNA sequences for bovine pituitary FGF. 30 U.S.P.Q.2d at 1481. Thus, neither the applicant nor the skilled artisan could have predicted what sequences would fall within the scope of the genus claim since a representative number of species were not provided to set the metes and bounds of the genus. In contrast, the present application discloses, by reference to the written out sequence, all of the sequences of the components of the claimed vector system. Thus, the metes and bounds of this genus are not in question.

Moreover, the Office Action again cites *The Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1566; 43 USPQ2d 1398, 1404 (Fed. Cir. 1997) (hereafter, "*Lilly*") to support the argument that the Applicants are attempting to define the nucleic acid sequences by a statement of function. However, the facts in *Lilly* are not applicable to the instant claims. Applicants in *Lilly* were attempting to claim human cDNA for human proinsulin while only

providing the sequence for the rat cDNA. 119 F.3d at 1566; 43 USPQ2d at 1404. As the sequence of human proinsulin was not known at the time that application was filed, the skilled artisan could not have known what was actually being claimed. The court therefore concluded that applicants were attempting to claim the coding sequence based only on an indication of what the gene does rather than what it is. In contrast, the present application discloses, by reference to the written-out sequence, all of the sequences of the components of the claimed vector system. It is therefore factually and legally incorrect to assert that the instant claims do not describe the genus by structure.

2. Moreover, the Board of Patent Appeals and Interferences (BPAI) has been very consistent when it comes to written description rejections of percent identity claims. A recent review of decisions by the BPAI revealed six cases where the Board reversed an examiner's written description rejection of a percent identity claim, and not a single instance where such a rejection was affirmed.[1]

In *Ex parte Sun,*[2] the examiner pointed out that the patent specification failed to disclose a single example of a wee1 variant retaining the activity of wee1 and sharing only 80% identity with the reference sequence, and "argued that the "specification does not set forth what specific structural or physical features define the claimed isolated nucleic acids,'" and "that one skilled in the art "could not predict the structure and function of isolated nucleic acids comprising a wee1 polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1.'" *Id.* at 7-8. The Board reversed the written description rejection, citing *Enzo II* and holding that the disclosure of the single reference sequence and methodology for screening for variants having Wee1 activity was sufficient to satisfy the written description requirement. *Id.* at 8-9, 11.

Likewise, in *Ex parte Bandman* ("*Bandman I*")[3] and *Ex parte Au-Young*,[4] the Board reversed written description rejections of claims encompassing any "naturally-occurring"

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[1] Christopher M. Holman, *Is Lilly Written Description A Paper Tiger?: A Comprehensive Assessment Of The Impact Of Eli Lilly And Its Progeny In The Courts And Pto*, 17 Alb. L.J. Sci. & Tech. 1, 44-47 (2007).
[2] Appeal No. 2003-1993, Application No. 09/470,526 (B.P.A.I.) – non-binding precedent
[3] Appeal No. 2003-1805, Application No. 09/079,892 (B.P.A.I.) – non-binding precedent
[4] Appeal No. 2003-1817, Application No. 09/501,714 (B.P.A.I.) – non-binding precedent

polynucleotide encoding an amino acid sequence sharing 90% identity to a disclosed reference sequence. *Bandman I* at 6-7. In both cases, the examiners' rejections were based on a determination that the disclosure provided no guidance as to how the sequences of naturally occurring alleles could be distinguished from non-naturally occurring sequences, and no way to predict they would all have function. *Id.* at 3. The Board disagreed, finding that 90% identity and "naturally occurring" were enough to adequately describe the genus, even without a functional limitation. *Id.* at 5.

Significantly, in *Ex parte Meyers*,[5] the Board reversed the written description rejection of a claim encompassing all nucleotide sequences having at least 70% identity with the reference sequence and encoding a polypeptide having dehydrogenase activity.

Moreover, in *Ex parte Bandman* (*Bandman II*),[6] the examiner supported a written description rejection of a claim encompassing any "isolated polynucleotide encoding ... a polypeptide comprising any naturally occurring amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:1." by pointing out that the specification provided only a single representative sequence and "no disclosure of any particular structure to function/activity relationship in the single disclosed species." *Id.* at 3. However, the Board reversed this rejection, faulting the Examiner for failing to provide adequate explanation or evidence to support the assertion that the specification failed to disclose any structure to function/activity relationship.

Most recently, in *Ex parte Smith*,[7] the Board reversed the written description rejection of a claim reciting a method that included a step of "adding isolated viral reaper protein having at least 50% sequence similarity to SEQ ID NO:2 and capable of inducing caspase activation in a vertebrate cell." *Id.* at 2 (emphasis added). Note that "similarity" encompasses not only identical residues, but also conservative amino acid substitutions, so the genus in this case is much broader than even 50% identity. However, the Board seemed to be impressed by the fact that in this case the specification described 15 variants of the reference viral reaper protein, sharing

[5] Appeal No. 2003-1820, Application No. 09/464,039 (B.P.A.I.) – non-binding precedent
[6] Appeal No. 2004-2319, Application No. 09/915,694 (B.P.A.I.) – non-binding precedent
[7] Appeal No. 2005-0147, Application No. 10/203,081 (B.P.A.I.) – non-binding precedent

between 62%-87% similarity to the reference sequence. *Id.* at 5. In the view of the board, this information amounted to a description of a relationship between structure and function, which under *Enzo II* can be used to satisfy the written description requirement in the absence of a literal disclosure of structure. *Id.* at 6-7.

3. Based on the above misapplication of the caselaw, the Office Action incorrectly alleged that the specification fails to disclose a representative number of species. For example, the Office Action states that besides the proteins encoded by the nucleotide sequence SEQ ID NO:1, the specification fails to disclose any variants of AAV4 Rep and AAV4 Capsid proteins. As noted above, this is incorrect since the specification and claims disclose amino acids having at least 90% sequence identity to the reference sequence. This is by definition a disclosure of all of the variants of the protein within the genus. What the Office Action must therefore intend by this statement is that Applicants have allegedly not exemplified any of these variants. This would, however, be legal error as the written description requirement does not require anything more than identifying the metes and bounds of the claim.

3. The Office Action further alleged that "the AAV4 capsid protein variants having at least 90% homology to an amino acid sequence set forth in SEQ ID NO:4 are not associated with any specific functional activity." The Office Action further states that "the variants fail to meet the USPTO written description guidelines because the invention as claimed fails to recite any specific functional limitation associated with structural variants." This is both factually and legally incorrect.

First, written description of a genus of amino acids can be satisfied by reference to percent identity without reciting a function. This is demonstrated in Example 11A of the new USPTO *Written Description Training Materials* ("Training Materials"; March 25, 2008 Rev. 1), wherein a claim to "an isolated nucleic acid that encodes a polypeptide with at least 85% amino acid sequence identity to SEQ ID NO:2" was concluded to satisfy the written description requirement. The Office Action does not provide any authority for its assertion to the contrary that a specific functional activity associated with the variant is required. Applicants have

therefore deleted reference to any functional limitation in claim 1. This amended claim clearly satisfies the written description requirement, since, as pointed out in the Training Materials, "[w]ith the aid of a computer, one of skill in the art could identify all of the nucleic acid sequences ..." (Example 11, page 38, first paragraph). Applicants therefore respectfully assert that the functional limitation is not necessary to provide written description or enablement for the claimed compositions within the recited scope.

Second, prior claim 1 did in fact include the functional limitation that "the vector system produces AAV particles." The Office Action, however, concluded that this is not a function of the Capsid protein but of the entire vector system. While this may be true, there are always additional factors relevant to any function. The importance of this limitation was to exclude Capsid proteins that were incapable of forming particles. The fact that other proteins are involved in the process is irrelevant if the process could fail with certain variants. This is true in even the simplest case. For example, the ability of protein A to bind protein B would presumably constitute a specific functional activity; and yet even protein binding is dependent upon other factors, such as pH, salt concentrations, temperature, etc. It therefore appears that the Examiner's concerns with this claim may be the phrasing "wherein the vector system produces AAV particles." Applicants have therefore added new claim 43, which is identical to amended claim 1 except that it further recites the functional limitation "wherein the capsid protein can form a transducing AAV particle." Support for this amendment is found at least on page 2, paragraph 2 and the paragraph bridging pages 3 and 4 wherein infection, transduction, and tissue tropism are disclosed as dependent upon the capsid protein. Moreover, transduction is both attributable to the capsid protein and easily measured by routine methods.

Knowledge available in the art at the time the application was filed in combination with the instant disclosure would have put the skilled artisan in possession of AAV4 variants within the claimed scope that have the ability to form a transducing AAV particle. In addition to the guidance provide by AAV2 deletion studies disclosed on page 2, paragraph 2, the skilled artisan could have aligned the sequence of AAV2 capsid protein (e.g., VP1) to that disclosed for AAV4 in order to determine the conserved regions. This would have guided the artisan to make only conservative mutations within these regions to avoid loss of the common function, i.e., the ability

to form particles. In other words, it is the non-conserved regions that are likely attributable to the unique properties of each capsid protein, such as tissue tropism, and it is the conserved regions that are likely attributable to the common properties, such as the ability to form particles. Thus, written description of this genus of amino acids is satisfied (see Example 11B of the Training Materials).

4. In response to these arguments, which were provided in Applicants response filed June 18, 2008, the Office in an Advisory Action asserted that the specification fails to disclose any variant that has the claimed functional properties, i.e., formation of transducing AAV particles with respect to 10% [sic] variation in SEQ ID NO:4. The Advisory Action further points to evidence that "removal or alteration of VP1 ... results in 'reduced yield of infectious particles'" and "mutations within the VP3 coding region result in the failure to produce any single-stranded progeny DNA or infectious particles." However, the Advisory Action is using evidence of intentional efforts to create non-functional mutants as evidence that variants within the claimed scope would be non-functional.

First, the fact that mutations within the AAV genome can inactivate gene expression or reduce particle yield is hardly surprising. For example, nonsense mutations resulting in stop codons would clearly terminate transcription and result in protein truncation, and gene deletions would have a similarly predictable result. However, mutations such as these are predictable.

Second, the section of the specification pointed to by the Advisory Action is citing reports detailing genetic analysis of AAV2 using targeted mutation to intentionally inactivate activity. These reports are hardly indicative of how the skilled artisan would make AAV4 variants as claimed. Specifically, Tratschin et al. (J Virol. 1984 Sep;51(3):611-9; attached as **Exhibit A**) and Hermonat et al. (J Virol. 1984 Aug;51(2):329-39; attached as **Exhibit B**) used restriction enzymes to create targeted insertions and deletions throughout the genome to identify phenotypes for each of the regions. This led to identification of the Rep and Cap reading frames based on the ability of the mutations to inhibit replication and particle formation, respectively. These reports, therefore, are not representative of the manner in which the skilled artisan would attempt to create functional AAV4 mutants. For example, the skilled artisan would be much

more likely to attempt to produce AAV4 variants within the claimed scope using missense mutations that avoid truncations or insertions.

Moreover, the Office is overlooking an important contribution made by the recited AAV2 mutation studies. By providing the sequence for AAV4, Applicants enabled the skilled artisan to analyze alignments of AAV2 and AAV4 in view of these mutation data in order to identify residues and motifs that are likely critical for function. Likewise, the skilled artisan could identify either variable or conserved regions between the two AAVs in order to select AAV4 variants within the claimed scope that would avoid predictable inactivation.

For example, in an alignment of the 534 amino acids in the VP3 protein of AAV2 and AAV4, 290 are conserved both in sequence and structure (beta barrel region). Another 119 are structurally conserved but differ in amino acid sequence (a total of 409). As disclosed in Wu et al. (Proc Int Conf Intell Syst Mol Biol. 1996;4:230-40; attached as **Exhibit C**), there were several known substitutions that were likely to not disrupt activity (e.g., FY, IV, ST, AS, DE, KR, DN, EQ, HY). If the skilled artisan wanted to make an AAV particle that had an amino acid sequence different from AAV4 but still had the same activity, they would be motivated to target the 409 amino acids with these conserved mutations since variable regions would likely be responsible for unique properties. One of these 14 amino acids occurs 294 times in the 409 structurally conserved amino acids. Thus, the skilled artisan could predictably mutate up to 55% of the amino acids in AAV4 VP3 and still have a functional particle. Many other such conservative mutations could be reasonable predicted based on routine skill.

In contrast, new claims 43-45 recite AAV4 capsid proteins having at least 90%, 95%, and 99% homology, respectively, to the reference sequence "wherein the capsid protein can form a transducing AAV particle." As discussed above, these claims are more conservative in scope to those in, for example, *Ex parte Sun*, where a single example of a wee1 variant combined with a methodology for screening functional variants was sufficient to satisfy the written description requirement for wee1 variants at 80% identity. Like these claims, however, Applicants have provided a suitable means for screening the variants, i.e., testing for formation particles that can transduce target cells. Applicants therefore respectfully assert that the skilled artisan would understand Applicants to be in possession of AAV4 variants within these ranges having the

ability to form a transducing AAV particle. Applicants therefore respectfully request the withdrawal of the rejection of these claims.

Applicants therefore respectfully request the withdrawal of this rejection and allowance of claims 2-3, 6-28, and 30-36, and 38-42 and new claim 43.

B. Claims 2-3, 6-28, and 30-36, and 38-42 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled.

The basis for this rejection appears to be two-fold. First, the Office Action asserts that the specification fails to disclose a representative number of species defined by structure and function as indicated in the written description rejection above.

Second, the Office Action asserts that screening variants wherein at least 10% of residues are added, substituted, and/or deleted at random is not routine in the art. For example, the Office Action states that the "applicant fails to point out where in the specification there is support for extensive making and testing of any and all natural and non-natural variants as claimed." Applicants presume that the term "extensive" is meant to refer to the amount of modification being made rather than the skill needed to test for activity, because the Office Action further states "the specification can not be relied on to teach how to make the variants as claimed." However, either conclusion would be erroneous. Applicants are not required to teach methods that are routine in the art, and the Office Action has provided no basis to conclude that the science of amino acid synthesis or nucleic acid recombination is anything other than routine in the art. The Advisory Action similarly states that "making and testing a point mutation is significantly different from ... making and testing ... amino acid sequences wherein at least 10% amino acids are added, deleted and/or substituted" and "the specification can not be relied on to teach how to make the variants as claimed." This is again unsubstantiated and untrue. While Applicants appreciate that extra effort is required to produce multiple mutations, this is hardly outside of routine skill. Applicants do not need to instruct the skilled artisan how to make nucleotide/amino acid substitutions to arrive at a protein covered by the claims.

Likewise, the testing of a particular capsid or Rep variant in a vector system to determine if it produces a transducing particle is no more or less complex than that for a single amino acid

mutation. Once an AAV4 capsid or Rep variant is produced, the methods for testing the ability of the variant to produce a functional AAV4 particle are also routine. Whether the experimentation necessary is undue therefore is a function of the predictability of identifying a single variant without resorting to further invention. In contrast, the Examiner appears to be suggesting that the skilled artisan should be enabled to produce an almanac of ALL of the functional AAV4 mutants without undue experimentation. Of course this can not be the standard. The purpose of the enablement requirement is for the Applicant to teach the skilled artisan how to practice the invention, i.e., produce a functional AAV4 particle using nucleic acids within the claimed scope. Evidence of some non-functional mutations within the claimed scope does not lead to the conclusion that a functional variant could not be identified using routine skill.

As noted above, the skilled artisan is guided by the specification and knowledge in the art for AAV2 to make modifications to capsid sequence that would result in a transducing particle by, for example, 1) conserving residues demonstrated to be important for AAV2 and 2) conserving residues that are variable between AAV2 and AAV4 and therefore likely to be important for unique tissue tropism. Thus, the information available in the art combined with the general predictability for maintaining function at sequence identities above 70% (see Tian, W. and Skolnick, J. J Mol Biol. 2003 Oct 31;333(4):863-82, of record) is such that the skilled artisan would be able to design a capsid protein having 90% sequence identity to the disclosed sequence for AAV4 capsid that is capable of assembling into a transducing viral particle. The Office Action has not provided any scientific or legal reasoning to contradict this position, but has instead made generalized statements regarding "the unpredictability of a particular area."

Applicants therefore respectfully request withdrawal of the instant rejection and allowance of claims 2-3, 6-28, and 30-36, and 38-42 and new claim 43.

Conclusion

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment submitted via EFS WEB authorizing payment in the amount of $1,860.00, representing $1,050.00 for the fee for a large entity under 37 C.F.R. § 1.17(a)(3) for a Three (3) Month Extension of Time and $810.00 for the Request for Continued Examination (RCE) fee for a large entity under 37 C.F.R. § 1.17(e), a Request for Continued Examination (RCE), and a Request for Extension of Time are hereby enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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